Eur J Clin Pharmacol (1997) 52: 135–138

PHARMACOKINETICS AND DISPOSITION

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Cerebrospinal fluid and plasma disposition of yohimbine and 11-hydroxy-yohimbine in young and older healthy subjects, and Alzheimer's disease patients

Received: 29 September 1995 / Accepted in revised form: 4 March 1996

Abstract *Objective*: The plasma and cerebrospinal fluid (CSF) disposition of yohimbine (YO) and 11-hydroxy-yohimbine (11-OH-YO), after oral administration of a single dose of YO (0.65 $mg \cdot kg^{-1}$) were studied in young and older healthy subjects and in patients with Alzheimer's disease (AD).
Results: Plasma disposition of YO displayed large variability; no significant differences among subject groups were observed. In contrast, 11-OH-YO C_{max} and AUC were significantly lower in the older normal subjects than in the young normal or AD subjects. A strong positive correlation between CSF and plasma YO concentrations was observed. A weak positive correlation between CSF and plasma concentrations of 11-OH-YO was also observed. CSF to plasma concentration ratios for yohimbine and 11-OH-YO were low (approximately 2%).

Key words Yohimbine, Alzheimer's disease; 11-hydroxy-yohimbine pharmacokinetics, plasma, cerebrospinal fluid, healthy subjects

Introduction

Yohimbine (YO), a selective α-2-adrenergic antagonist, is an accepted chemical probe for differentiating α-receptor subtypes [9]. Clinically, YO is an approved drug for the management of impotence [18], but must be used with caution in patients with co-existing hypertension [11]. YO is also used in the treatment of orthostatic hypotension, secondary to autonomic failure [21], tricyclic antidepressant therapy [14], dry mouth [6, 1] and to induce lipid mobilization in obese subjects [3]. YO could also be used as a probe to characterize sympathetic reactivity in essential hypertension [10], and potential vulnerability to affective and anxiety disorders [18]. It is also of interest as a pharmacologic probe of the central noradrenergic system, in light of recent studies showing an increase in cerebrospinal fluid (CSF) levels of norepinephrine (NE) during normal ageing [24] and further increased CSF NE levels in advanced Alzheimer's disease [24].

The pharmacokinetics of YO have only been studied in young healthy subjects [12, 13, 15, 21] or in middle-aged patients treated with antidepressant drugs [2]. These studies have shown that YO is rapidly eliminated from the plasma (apparent elimination half-life between 0.5 and 1 h) and has a high and variable plasma clearance. Following oral administration, the systemic bioavailability is approximately 30% and the absorption rate is high (T_{max} between 10 and 45 min) [12, 15]. In addition, we have shown that YO has at least two metabolites: 10-hydroxy-yohimbine (10-OH-YO) and 11-OH-YO [15]. The 11-hydroxy metabolite is largely present in plasma and exhibits a longer elimination half-life (approximately 6 h) than YO. This metabolite is of interest because it possesses α-2-adrenergic antagonist properties [4].

In this current study of the α-2 regulation of central and peripheral noradrenergic systems, we compared the disposition of YO and 11-OH-YO in CSF and plasma in young and older normal subjects and in patients with AD.

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Subjects and methods

Subjects

The current work is derived from a study of the effects of Alzheimer's disease and advanced age on the α-2 regulation of central

and peripheral noradrenergic systems [22]. This study was approved by the Human Subjects Review Committee of the University of Washington and written informed consent was obtained from all subjects and from the AD patients' next of kin. All subjects were nonsmokers, had normal hepatic and renal function, and were free of all medication for at least 1 month prior to study. The subjects who entered the study were: 11 young normal subjects [11 male, 26.3 (4.8) years, mean with (SD)] 10 older normal subjects [6 male, 4 female, 71.2 (3.5) years] and 10 AD patients [7 male, 3 female, 69.5 (7.9) years].

Study design

Subjects fasted overnight and received a single oral dose of YO (0.65 $mg \cdot kg^{-1}$) at approximately 0900 hours. Blood was collected just prior to administration of YO and at 0.5, 1, 1.5, 2, 2.5 and 3 h thereafter. CSF was collected 90 min following YO administration by lumbar puncture with the subject in the lateral decubitus position. Plasma and CSF samples were stored at −70 °C until analysis.

Analytical methods

YO and its hydroxylated metabolites in the CSF and in the plasma were assayed using a normal-phase high-pressure liquid chromatography method with fluorimetric detection [15]. The limits of determination for YO, 10-OH-YO and 11-OH-YO were 0.1, 0.5 and 1.0 $ng \cdot ml^{-1}$, respectively. The between-day reproducibilities were 3.8, 1.4 and 5.9%, respectively.

Pharmacokinetic and statistical analyses

Peak concentration (C_{max}), corresponding time-to-peak concentration (t_{max}) and AUC from zero to 3 h (AUC(0–3 h)) were derived from the raw data. Differences among subject groups were evaluated by one-way analysis of variance (ANOVA). Following a significant ANOVA, post-hoc comparisons were made using Fisher's least significant difference test. Correlations between CSF and plasma levels of YO and 11-OH-YO were determined by Pearson's correlation coefficient (r). The statistical significance from zero of the slope of the regression was checked by ANOVA. A value of $P < 0.05$ defined statistical significance. All data are presented as mean with standard deviation (SD).

Results and discussion

Drugs undergoing extensive first-pass metabolism can display significant inter-individual variations in drug concentrations, even in young healthy subjects [27], as well as significant intra-individual variations in elimination, as evidenced by variation in elimination rate constants [28]. YO, which also undergoes extensive first-pass metabolism, displayed a highly variable disposition, particularly in the young and older normal subjects (Table 1). That the lowest variability was found in the AD patient group may either have resulted from chance or reflect a greater within-group homogeneity from a metabolic standpoint. Indeed, decreased clearance of YO to 11-OH-YO has been shown to be under genetic control, co-segregating with the debrisoquine oxidative polymorphism (R. Le Verge 1994, unpublished observation). The metabolic status of subjects in the present study was unknown. Such variability in YO disposition should lead to variability in pharmacodynamics. Determination of the metabolic status of subjects (e.g., by using a debrisoquine challenge test) could decrease experimental variability in studies in which YO is used as a pharmacologic probe. In accordance with results from our previous study, 10-OH-YO was not detected in any plasma sample, or in any CSF sample.

In contrast to YO, the plasma disposition of 11-OH-YO, which is not further metabolized [15], displayed low inter-individual variability, with a maximal three-fold variation in AUC(0–3 h) within subject groups. The lower C_{max} and AUC (0–3 h) of 11-OH-YO in the older normal subjects compared with young subjects are consistent with decreased metabolism secondary to age effects on hepatic blood flow [26]. Thus, YO metabolite disposition in AD subjects appears unusual, but is consistent with the corresponding YO disposition data.

The delivery of drugs via plasma to the brain and the CSF is hindered by the presence of tight junctions between the endothelial cells of blood microcapillaries, the absence of transport vesicles, and by the fact that the

Table 1 Mean (SD and range) disposition data in plasma and cerebrospinal fluid for yohimbine and 11-hydroxy-yohimbine in normal young subjects, normal old subjects and Alzheimer's patient. The difference is statistically significant between young healthy subjects and old healthy subjects (a), old healthy subjects and Alzheimer patients (b) and young healthy subjects and Alzheimer's patients (c)

		Yohimbine			11-Hydroxy-yohimbine		
		Cmax (μg/l)	AUC (0–3h) (μg/l)	CSF level (μg · h/l)	Cmax (μg/l)	AUC (0–3h) (μg · h/l)	CSF level (μg/l)
Young healthy subjects	Mean	421	504	2.9	411 a	793 a	7.7 a,c
	SD	350	435	2.8	149	254	2.3
	(range)	55–1119	74–1325	0.1–9.2	244–813	514–1439	4.1–12.0
Old healthy subjects	Mean	518	981	7.7 a,b	236 b	491 b	4.6
	SD	374	818	6.2	87	191	2.3
	(range)	33–1075	54–2169	0.1–19.1	119–354	247–764	1.9–9.3
Alzheimer patients	Mean	339	446	3.2	373	710	4.5
	SD	148	205	1.5	114	226	1.3
	(range)	135–527	173–713	0.4–5.5	154–559	354–948	2.3–6.9

capillary walls lack water-filled channels of suitable size for entry of hydrophilic molecules by aqueous diffusion [7]. Transfer across the blood-brain barrier takes place mainly or exclusively through two processes: dissolution in and diffusion through the lipid membranes and cytoplasm of the endothelium (transcellular diffusion), and combined carrier-mediated and diffusional transport across these structures [8]. The ability of low-molecular-weight drugs (MW less than 400 Da) to cross the blood-brain barrier can be correlated with their lipophilicity (formerly expressed in the lipid/water partition hypothesis) [19, 25]. However, notable deviations have been reported [5]. The rate of blood-brain transfer of a drug may be limited by blood flow, by blood-brain barrier permeability according to its lipid/water partition or by protein binding.

Significantly higher CSF concentrations were found for YO in older normal subjects compared with young normal and AD subjects, and for 11-OH-YO in young normal compared with older normal and AD subjects. However, the interpretation of these differences should be made with caution for three reasons: (1) these CSF concentrations were single-point measures; (2) there were also trends toward differences in plasma disposition of YO among groups; and (3) the protein binding has not been determined. Furthermore, the trend towards a slower apparent elimination rate of YO in the old subjects compared with that in the young subjects (Fig. 1) may result in differences in CSF concentration profiles [7].

There was a strong positive linear correlation ($r = 0.9678$, $P = 0.0001$) between CSF YO and the corresponding plasma YO concentration (Fig. 2 Top): the slope (95% C.I.) of the regression line was 0.0177 (0.0164–0.0190). This robust correlation suggested a first-order transfer rate of YO through the blood-brain barrier. The CSF/plasma concentration ratio was rather small and was not significantly different among groups, suggesting that age and AD may not influence this parameter.

A weaker positive correlation ($r = 0.4159$, $P = 0.0024$) was found for CSF and plasma concentrations of 11-OH-YO (Fig. 2 Bottom): the slope of the regression line was 0.0091 (0.0034–0.0147). This weak correlation seems inconsistent with the lower variability of the plasma disposition of 11-OH-YO and of the CSF/plasma con-

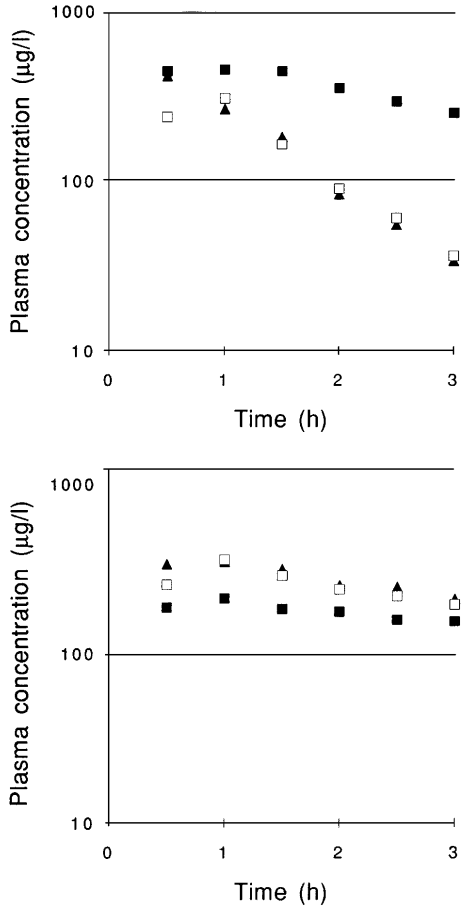

Fig. 1 Mean plasma concentration time-curves (µg/l) of yohimbine (top) and of 11-hydroxy-yohimbine (bottom) in normal young subjects (empty square), normal old subjects (full square) and Alzheimer's patients (full triangle)

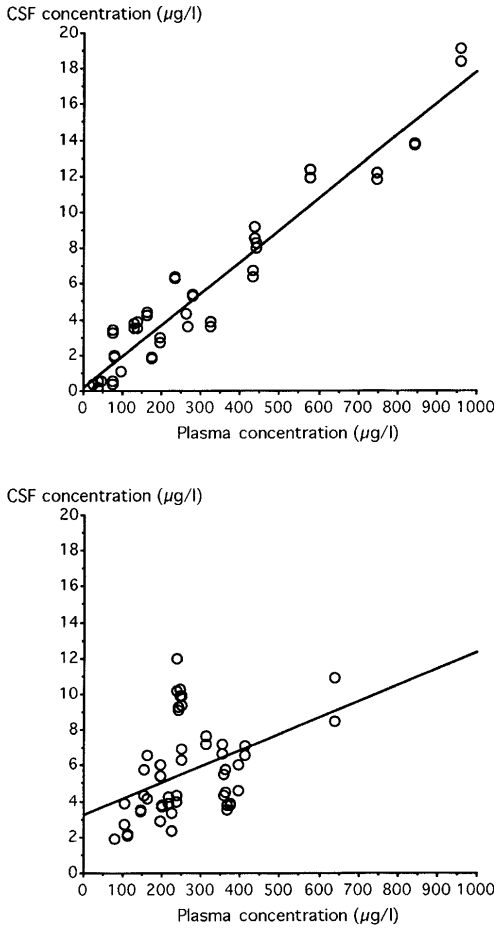

Fig. 2 Correlation between cerebrospinal and plasma concentrations (µg/l) of yohimbine (top) and of 11-hydroxy-yohimbine (bottom) in normal young subjects, normal old subjects and *Alzheimer's* patients

centration ratios compared with those of YO. Thus, this may suggest that another factor (in addition to plasma 11-OH-YO concentration) might contribute to CSF 11-OH-YO concentrations. Such a factor might be CNS metabolism of YO. Indeed, the presence of metabolizing phase 1 and phase 2 enzymes in animal cerebral microvessel endothelial cells is evidence for the ability of the cells constituting the blood-brain barrier to limit drug entry into the brain by carrying out biotransformation reactions [16].

In summary, the current study has demonstrated that transfer across the blood-brain barrier for both YO and 11-OH-YO was rather low. However, the extent of blood-brain barrier crossing was correlated only with total plasma concentrations of YO and did not appear to be altered by age or AD. Furthermore, CSF and plasma disposition of YO displayed fairly large variability, in contrast to that of 11-OH-YO.

Because 11-OH-YO has α-2-adrenergic antagonist properties compatible with a pharmacologic effect and different pharmacokinetic behavior than YO, with lowest variability and longer elimination half-life, this drug deserves further investigation.

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